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Specific progressive cAMP reduction implicates energy deficit in presymptomatic Huntington's disease knock-in mice.

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Defects in gene transcription and mitochondrial function have been implicated in the dominant disease process that leads to the loss of striatal neurons in Huntington's disease (HD). Here we have used precise genetic HD mouse and striatal cell models to investigate the hypothesis that decreased cAMP responsive element (CRE)-mediated gene transcription may reflect impaired energy metabolism. We found that reduced CRE-signaling in Hdh(Q111) striatum, monitored by brain derived neurotrophic factor and phospho-CRE binding protein (CREB), predated inclusion formation. Furthermore, cAMP levels in Hdh(Q111) striatum declined from an early age (10 weeks), and cAMP was significantly decreased in HD postmortem brain and lymphoblastoid cells, attesting to a chronic deficit in man. Reduced CRE-signaling in cultured STHdh(Q111) striatal cells was associated with cytosolic CREB binding protein that mirrored diminished cAMP synthesis. **Moreover, mutant cells exhibited mitochondrial respiratory chain impairment, evidenced by decreased ATP and ATP/ADP ratio**, impaired MTT conversion and heightened sensitivity to 3-nitropropionic acid. Thus, our findings strongly suggest that impaired ATP synthesis and diminished cAMP levels amplify the early HD disease cascade by decreasing CRE-regulated gene transcription and altering energy dependent processes essential to neuronal cell survival.

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Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) triggered by valproate therapy.

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We report in this study a patient who developed repeated convulsions as a result of valproate therapy. MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) was subsequently diagnosed and a nucleotide 3243 A-->G mutation was detected in the mitochondrial DNA. This mutation predisposes the patient to the detrimental effects of valproate on oxidative phosphorylation. CONCLUSION: We support the suggestion of Ponchaut et al. [14] that valproate should not be given to patients suspected of having mitochondrial diseases. In addition, for patients whose seizures worsen with valproate therapy, an inborn error of mitochondrial metabolism should be suspected. The underlying mitochondrial DNA defects should be sought for family screening and genetic counselling.

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Mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure.

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We report on 3 siblings (2 females and 1 male) with chronic progressive external ophthalmoplegia (CPEO), compatible with inherited mitochondrial cytopathy. The younger of the two sisters died at the age of 37 due to progressive respiratory failure. The older one presented with a status epilepticus at the age of 39 and was treated with valproate. Five months after the start of treatment, she developed fulminant liver failure and died. The brother has suffered from CPEO since early childhood but has had so far no other symptoms of a mitochondrial disease. A muscle biopsy from the younger sister revealed ragged-red fibers and decreased activities of complex I and IV of the respiratory chain but no pathogenic mutations in the mitochondrial tRNA genes or in several locations in the coding region of the mitochondrial genome. In the older sister's liver (obtained post-mortem), mitochondrial DNA was fragmented and could not be investigated. The clinical presentation and the biochemical findings suggest that all 3 siblings suffered from a mitochondrial cytopathy. Since mitochondrial cytopathies and valproate-induced fulminant liver failure are both rare events, an association between them is likely. Mitochondrial diseases should therefore be considered as a risk factor for valproate-induced liver failure and be excluded before treatment with valproate.